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By: Karen A. Herrand
Karen A. Herrand

Docket No.: 0656-008US6

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

APPLICANT:	Skiffington et al.	EXAMINER:	Beisner, William H.
REISSUE SERIAL NO.:	10/014,154	ART UNIT:	1744
FILED:	December 6, 2001		
ORIGINAL PATENT NO.:	6,180,395		
ORIGINAL PATENT ISSUE DATE:	January 30, 2001		
TITLE:	Reagent Chamber for Test Apparatus and Test Apparatus		

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Alexandria, VA 22313-1450

RESPONSE TO NOITCE OF NON-COMPLIANT APPEAL BRIEF

In response to the Notice of Non-Compliant Appeal Brief mailed January 10, 2007, applicant/appellant submits an amended Appeal Brief. Applicant respectfully requests that the original appeal brief (mailed October 12, 2006) be replaced with the enclosed Appeal Brief, and that all exhibits filed on October 12, 2006, be transferred to the enclosed Appeal Brief.

A petition for an extension of time (one month) and the required fees are enclosed as indicated in the accompanying Transmittal and Fee Transmittal forms. Please charge any outstanding fees or credit any overpayments to Deposit Account No. 50-1895, Ref. No. 0656-008US6.

Respectfully submitted:

Date: March 9, 2007

Leslie Meyer-Leon
Leslie Meyer-Leon
Reg. No. 37,381

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Reissue Serial No:	10/014,154	Art Unit:	1744
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APPEAL BRIEF

This is an appeal from the final rejection of claims 1, 2, 5-7, 10, 12, 14, 15, 17-19, 23, 24 and 26 of the Office Action dated January 31, 2006. Appellant submits this Appeal Brief pursuant to 35 U.S.C. §134 and 37 CFR §41.37.

Table Of Contents

I. Real Party in Interest

The real party in interest is Charm Sciences, Inc., the assignee of record, which is a corporation of the Commonwealth of Massachusetts having a principle place of business at 659 Andover Street, Lawrence, MA 01843.

II. Related Appeals And Interferences

There are no appeals or interferences related to the present appeal.

III. Status of Claims

Claims 1, 2, 4, 5-7, 10, 12, 14, 15, 17-19, 23, 24, 26, and 30 are pending in the application. Claims 4 and 30 are allowed. Claims 3, 8, 9, 11, 13, 16, 20-22, 25, 27-29, and 31-45 are cancelled. Claims 1, 2, 5-7, 10, 12, 14, 15, 17-19, 23, 24 and 26 stand rejected and are involved in this appeal.

IV. Status of Amendments

There have been no amendments filed after the final rejection of January 31, 2006.

V. Summary of Claimed Subject Matter

A. Overview of the Invention

The invention contributes to the field of hygiene monitoring by providing a portable, inexpensive device for rapid on-site measurement of luminescence, as an indication of ATP content in a swabbed test sample. Original Patent, col. 1, lines 30-39; col. 12, lines 1-8. To be suitable for on-site use, such a device must be self-equipped with a swab for collecting the test sample and with all of the reagents for detecting ATP, including a detergent-containing lysis solution to extract ATP from a mixed population of cellular contaminants, and reagents for performing a luciferin-luciferase reaction. Id., col. 4, lines 43-52. Liquid and dry reagents must be sequestered in the device in a way that preserves their stability (id., col. 2, lines 47-51; col. 4, lines 23-24), and must be housed so as to make each reagent available in proper reaction sequence. Id., col. 4, lines 20-21. As the luciferin-luciferase reaction takes place in a homogeneous liquid reaction medium, the device must have a closed bottom end to house the liquid reaction without risk of leakage. The results of the luciferin-luciferase assay are determined by measuring luminescent output, so again the bottom of the device must remain closed to prevent leakage of liquid reactants into the luminometer instrument, and must

also be transparent so that luminescence can be emitted freely from the sample medium through the walls of the test unit to a photomultiplier tube. Id., col. 10, lines 58-60 and Fig. 5G.

The test apparatus of the invention meets these needs by generally including an elongated housing, a transparent test unit portion with a closed bottom end, one or more unit dose reagent chambers in either or both of the housing and test unit, and a moveable probe which swabs sample, releases reagent from the reagent chambers down into the bottom of the device, and aids admixture of sample and reagents in the bottom end of the test unit. Id., col. 2, lines 24-33; col. 6, lines 25-32; col. 10, lines 62-67; col. 11, lines 37-59. Results are then measured with the aid of a luminometer. Id., col. 6, lines 32-33; col. 8, lines 28-33, 35-38. In some embodiments, the test unit is a detachable portion of the test apparatus, in which case the bottom test unit portion of the test apparatus becomes a self-contained device, detachable from the test apparatus for insertion into the luminometer. Id., col. col. 10, lines 58-60; col. 11, lines 60-67; Fig. 5G.

B. Reference Citations to Specification

The following concise explanation of the subject matter is organized in claim groups corresponding to each independent claim and to each dependent claim argued separately below. In particular,

(1) claims 14, 15, 17-19, and 24 (test apparatus with test unit and reagent chamber);

(2) claims 5 and 6 (test apparatus with reagent chamber);

(3) claims 7 and 10 (test apparatus with reagent chamber and test unit);

(4) claims 23and 26 (detachable test unit with reagent chamber); and

(5) claims 1, 2, and 12 (reagent chamber adapted for use in ATP detection apparatus).

1. Claims 14, 15, 17-19, and 24 (test apparatus with test unit & reagent chamber)

Claim	Explanation and Support
14. A test apparatus for the detection of adenosine triphosphate (ATP) in a test sample, by luminescence, which test apparatus comprises:	Claim 14 is directed to a test apparatus adapted for luminescent detection of ATP in a test sample. col. 6, lines 19-24.
a) a longitudinal test apparatus housing	The test apparatus has a longitudinal (elongated)

Claim	Explanation and Support
having a one end and an other end;	housing with two opposing ends. col. 3, lines 5-10; col. 4, line 38
b) a moveable probe within the housing to collect a test sample and arranged to puncture a membrane seal;	The test apparatus includes a probe which moves longitudinally within the housing to collect a test sample and to puncture at least one membrane seal. col. 11, lines 45-52.
c) a transparent test unit having a one end and a closed bottom end extending from the one end of the housing for use in detecting luminescence in the test sample, and a first reagent composition to detect adenosine triphosphate (ATP), by luminescence, at the closed bottom end; and	Extending from one end of the longitudinal housing of the test apparatus is a test unit portion of the test apparatus, for use in detecting luminescent emissions from the test sample. The test unit is transparent. The test unit has a closed bottom end. At least one reagent is housed in the closed bottom end of the test unit which is a reagent to further the luminescent detection of ATP. col. 3, lines 5-10; col. 3, lines 40-47; col. 6, lines 25-32 and lines 48-53; col. 4, lines 33-36; col. 11, lines 1-3.
d) one or more unit dose reagent chambers longitudinally-positioned in the test unit, which reagent chamber comprises:	The test apparatus further includes one or more unit dose reagent chambers, at least one of such chambers positioned in the test unit portion of the test apparatus. The unit dose reagent chambers are longitudinally-positioned in the test unit portion of the test apparatus. col. 3, lines 5-10 and lines 55-65; col. 7, lines 30-37; col. 10, lines 41-43.
i) a cylinder having a one open end and an other opposite open end;	The unit dose reagent chamber is characterized by generally cylindrical side walls and opposing open ends. col. 7, lines 37-43; col. 9, lines 14-15
ii) a probe-puncturable membrane seal at and over the one end and the other end of the cylinder to form a sealed compartment; and	Both otherwise open ends of the reagent chamber are sealed by a membrane to form a sealed compartment. The membrane seal is frangible to puncture by the moveable probe which is longitudinally positioned within the test apparatus portion of the housing. col. 4, lines 10-20; col. 9, lines 16-18, 19-20;

Claim	Explanation and Support
	col. 17, lines 7-10
iii) a second reagent composition for use in the detection of adenosine triphosphate (ATP) in the test sample and sealed within the sealed compartment, which reagent composition comprises a buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for subsequent reaction with the first reagent composition.	At least one reagent is housed within the sealed compartment of the reagent chamber. The at least one reagent is a buffered solution for facilitating the extraction of ATP from the test sample into the buffered solution. Consistent with 14(c), above, the ATP-containing buffered solution is then dispelled to the closed bottom end of the test unit, where it is admixed with the first reagent, together forming a liquid reaction medium for the luciferin-luciferase reaction, and luminescent detection of ATP through the transparent walls of the closed bottom end of the test unit. col. 10, lines 62-67; col. 12, lines 30-39.
15. The apparatus of claim 14 wherein the membrane seal comprises aluminum foil.	In one embodiment, the reagent chamber can be sealed with an aluminum foil seal. col. 9, line 17; col. 17, line 7-10
17. The apparatus of claim 14 wherein the test unit has an open top end and a closed bottom end and is detachably secured to one end of the test apparatus.	In one embodiment, the test unit is detachably secured to the one end of the test apparatus from which it extends. Once detached from the test apparatus, the test unit has an open top end and a closed bottom end. col. 3, lines 5-10; col. 6, lines 39-49.
18. The apparatus of claim 14 wherein the one end of the test unit is sealed with a probe-puncturable membrane.	In one embodiment, an end of the test unit, opposed to the closed bottom end, can be sealed with a probe puncturable membrane. col. 10, lines 9-12.
19. The apparatus of claim 14 wherein the sealed compartment comprises a buffer-detergent solution and a luciferase and a luciferin substrate, as a reagent, is at the bottom end of the test unit.	In one embodiment, the sealed compartment contains a buffer-detergent solution. The test unit contains luciferase reagent and a luciferin substrate reagent in the closed bottom end of the test unit. col. 12 (example 1)
24. The apparatus of claim 19, wherein	In one embodiment, luciferase and luciferin reagents are housed in the closed bottom end of

Claim	Explanation and Support
said luciferase and said luciferin reagent are in tablet form.	the test unit portion of the test apparatus. col. 12 (example 1)

2. Claims 5 and 6 (combined test apparatus with reagent chamber)

Claim	Explanation and Support
5. In combination, the chamber of claim 1 in a test apparatus for the detection of adenosine triphosphate (ATP) in a test sample,	Claim 5 is directed to a combination device resulting from assembly of one or more of the unit dose reagent chambers of claim 1 into the ATP detection test apparatus for which it was designed. As a dependent claim, claim 5 incorporates all of the limitations of claim 1, and so the test apparatus of claim 5 must be adapted to conducting a luminescent-type reaction for detecting ATP in a test sample, and must also employ a moveable probe to obtain a test sample and to release one or more reagents from within a unit dose reagent chamber to a test unit. col. 5, lines 48-52; col. 6, lines 19-24; col. 11, lines 4-14.
wherein the reagent composition is a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing,	The combination test apparatus of claim 5 has, within the sealed compartment of its reagent chamber, a detergent-containing buffered solution formulated to release ATP from the test sample into the solution. This buffered solution then becomes the testing medium in the ATP detection reaction. col. 4, lines 23-36; col. 5, lines 48-52.
which test apparatus includes a luciferin-luciferase reagent for reaction with the released adenosine triphosphate (ATP) in the solution.	The test apparatus further includes a luciferin-luciferase reagent which reacts with any ATP released from the test sample into the buffered solution. col. 12 (example 1)
6. The combination of claim 5 wherein the test apparatus further comprises a longitudinally moveable probe to puncture the	The moveable probe of the combination test apparatus of claim 5 moves longitudinally within the within the test apparatus and performs its function of releasing reagents from the reagent chamber to the test unit by

Claim	Explanation and Support
membrane seals.	puncturing at least one membrane seal. col. 8, line 65 to col. 9, line 3; col. 10, lines 46-51.

3. Claims 7 and 10 (combined test apparatus with reagent chamber and test unit)

Claim	Explanation and Support
7. The combination of claim 5 wherein the test apparatus further comprises a closed bottom end, transparent test unit at the one end of the test apparatus, and wherein one or more unit dose reagent chambers are longitudinally positioned in the test unit.	The combined test apparatus of claim 5 includes at one end a test unit having a closed bottom end. The test unit is transparent. The unit dose reagent chambers are longitudinally-positioned in the test unit portion of the test apparatus. col. 3, lines 5-10; col. 7, lines 30-37; col. 10, lines 41-43.
10. The combination of claim 7 wherein the reagent composition is a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing and wherein said test apparatus includes a luciferase and a luciferin reagent at the bottom end of the test unit.	The luciferin-luciferase reagent in the combined test apparatus is present in the bottom end of the test unit portion of the test apparatus. col. 10, line 61-col. 11, line 3; col. 12 (example 1).

4. Claims 23 and 26 (detachable test unit)

Claim	Explanation and Support
23. A transparent test unit for use in a test apparatus for the detection of a test sample, which test unit comprises:	Claim 23 is directed to a transparent test unit, which includes features by which it can be detachably secured to a test apparatus for the detection of a test sample. One preferred embodiment of the test unit of claim 23 is the "unit dose containment system 49", shown in Fig. 7. col. 6, lines 38-48; col. 9, lines 12-14.

Claim	Explanation and Support
a one end; a closed bottom end; a probe-puncturable membrane over the one end;	The test unit has two ends, a one end which is sealed with a probe puncturable membrane, and an other end which is at the bottom of the test unit. The bottom end of the test unit is closed. col. 10, lines 9-12 and 38-40; col. 11, lines 26-29.
and the one end having **means for detachably securing** the test unit to the test apparatus	The one end of the test unit further includes those structure(s) and material(s) which function to secure the test unit to a test apparatus in a non-permanent, i.e., detachable, manner. Such structures and materials are, e.g., threads, a slidable fit, a weakened mechanical section, tape, a twistable fit (col. 6, lines 38-48), structural and material features known to those skilled in the art to be characteristic of a microtube having a removable cap (col. 9, lines 50 and Fig. 4), ridges and finger grips (col. 10, lines 2-6; col. 11, lines 60- 67 and Fig. 4, Fig. 5); peripheral indentation and finger grips 64 (col. 11, lines 20-25 and Fig. 8).
and the test unit having one or more unit dose reagent chambers, which unit dose chamber comprises:	The test unit further includes at least one reagent chamber. Fig. 7
a) a cylinder having a one open end and an other opposite open end;	The unit dose reagent chamber is characterized by generally cylindrical side walls and opposing open ends. col. 9, line 14-15.
b) a probe-puncturable membrane seal over the one end and the other end of the cylinder to form a sealed compartment: and	Both otherwise open ends of the reagent chamber are sealed by a membrane to form a sealed compartment. The membrane seal is frangible to puncture by a probe. col. 9, lines 15-18; col. 11, lines 7-9.
c) a reagent composition for use in the detection of the test sample and sealed within	At least one reagent is housed within the sealed compartment of the reagent chamber.

Claim	Explanation and Support
the sealed compartment;	col. 4, lines 24-33; col. 9, lines 14-18.
and wherein the test unit includes a luciferin-luciferase reagent.	A luciferin-luciferase reagent is included within the test unit. col. 3, lines 55-65.
26. The test unit of claim 23, wherein said luciferin-luciferase reagent is a luciferin-luciferase tablet.	In one embodiment, the luciferin-luciferase reagent can be contained within the test unit in the form of a tablet. col. 3, line 63.

5. Claims 1, 2, and 12 (reagent chamber)

Claim	Support
1. A unit dose reagent chamber for use in a test apparatus for the detection of adenosine triphosphate (ATP) in a test sample, and wherein a moveable probe is employed to obtain a test sample and to release reagents from the reagent chamber to a test unit, which unit dose chamber comprises:	The unit dose reagent chamber of claims 1, 2, and 12 contains an adenosine triphosphate (ATP) detection reagent and is designed to be suitable for assembly into an ATP detection test apparatus equipped with a moveable probe that is used to obtain the test sample and to release the ATP detection reagent from the reagent chamber into a test unit. col. 1, lines 40-43; col. 3, line 66-col. 4, line 9; col. 5, lines 48-52; col. 7, lines 30-37.
a) a cylinder having a one open end and an other opposite open end;	The unit dose reagent chamber is characterized by generally cylindrical side walls and opposing open ends. col. 9, lines 14-15.
b) a probe-puncturable membrane seal over the one end and the other end of the cylinder to form a sealed compartment; and	Both otherwise open ends of the reagent chamber are sealed by a membrane to form a sealed compartment. The membrane seal is frangible to puncture by the moveable probe which is longitudinally positioned within the test apparatus portion of the housing. col. 4, lines 10-20; col. 9, lines 16-18, 19-20; col. 11, lines 7-9; col. 17, lines 7-10.

Claim	Support
c) a reagent composition within the sealed compartment, which composition consists essentially of and is selected from the group consisting of:	At least one of two reagents is housed within the sealed compartment of the reagent chamber. col. 12 (example 1).
i) a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing; and	One of the reagents that can be contained within the sealed compartment is a detergent-containing buffered solution for facilitating the extraction of ATP from the test sample into the buffered solution. That buffered-solution then becomes the liquid medium for the testing reaction. col. 7, lines 57, 59; col. 10, lines 65-66; col. 12, line 31-39.
ii) a luciferin-luciferase reagent.	The other reagent that can be contained within the sealed compartment is a luciferin-luciferase reagent. col. 6, lines 19-24; col. 7, lines 60-64; col. 12, lines 50-55.
2. The chamber of claim 1 wherein the membrane seal comprises aluminum foil.	In one embodiment, the reagent chamber can be sealed with an aluminum foil seal. col. 9, line 17; col. 17, line 7-10.
12. The chamber of claim 1, wherein the reagent composition is selected from the group consisting of i) a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing; and ii) a luciferin-luciferase reagent, and wherein the reagent composition includes a biological buffer solution to optimize a reaction for the detection of adenosine triphosphate (ATP).	In one embodiment, the reagent composition chosen for containment within the sealed compartment includes a biological buffer solution having characteristics conducive to providing an optimal reaction medium for an ATP detection assay. col. 10, line 66-col. 11, line 3; col. 12, lines 50-55.

VI. Grounds of Rejection To Be Reviewed On Appeal

A. Whether claims 1, 2, 5-7, 10 and 12 are unpatentable under 35 U.S.C. § 103(a) over Bernstein (US 4,770,853; "Bernstein") in view of Simpson et al. (EP 0 309 184; "Simpson et al.") and Rich et al. (US 3,666,631; "Rich et al.").

B. Whether claims 10, 14, 15, 17-19, 23, 24 and 26 are unpatentable under 35 U.S.C. § 103(a) over Bernstein (US 4,770,853) in view of Simpson et al. (EP 0 309 184; "Simpson et al.") and Rich et al. (US 3,666,631; "Rich et al.") and taken further in view of Matsumoto et al. (JP 7-59555).

VII. Argument

A. The examiner's rejection of claims 1, 2, 5-7, 10 and 12 under 35 U.S.C. § 103(a) as not being patentable over Bernstein (US 4,770,853; "Bernstein") in view of Simpson et al. (EP 0 309 184; "Simpson") and Rich et al. (US 3,666,631; "Rich") should be reversed.

Claims 1, 2, 5-7, 10 and 12 stand rejected under 35 U.S.C. § 103(a) as unpatentable over Bernstein (US 4,770,853; "Bernstein") in view of Simpson et al. (EP 0 309 184; "Simpson et al.") and Rich et al. (US 3,666,631; "Rich et al."). Applicant respectfully requests that the rejection be reversed.

The examiner must establish factual basis for obviousness to a preponderance of the evidence, by determining the scope and content of the prior art, identifying the differences between the prior art and the claimed invention as a whole, determining the level of skill in the art, and providing factual support for finding a greater than 50% likelihood that one of ordinary skill in the art would not merely have been motivated to solve the problem, but would have been motivated to arrive at the same solution as that claimed. Facts established by rebuttal evidence must be evaluated along with the facts on which the conclusion of a prima facie case was reached, not against the conclusion itself. In other words, each piece of rebuttal evidence should not be evaluated for its ability to knockdown the prima facie case. All of the competent rebuttal evidence taken as a whole should be weighed against the evidence supporting the prima facie case. *In re Piasecki*, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984); MPEP 716.01(d).

The examiner has not met that burden. First, the examiner has not taken all claim limitations into account, and thus has not considered the invention as a whole. Second, as demonstrated by the Second Declaration of Steven J. Saul (Exhibit A) and the Childs et al. patent (Exhibit B), it has not

been established to a preponderance of the evidence that the skilled artisan would find a suggestion or motivation in the references to modify the Bernstein apparatus according to the disclosures of Simpson and Rich. As testified to by Dr. Saul, one of ordinary skill in the art in 1995, reading the Bernstein, Simpson, and Rich patents, would not have been motivated to provide a unit dose reagent chamber containing a luciferin-luciferase reagent by placing luciferin-luciferase in the vessel of the Bernstein apparatus, because the Bernstein apparatus is not suitable for chemiluminescent detection of ATP, and because modification of the Bernstein apparatus for chemiluminescent detection of ATP would have made the Bernstein apparatus unsuitable for its intended purpose of a solid phase immunodiffusion assay. Dr. Saul further testifies that one of ordinary skill in the art in 1995, reading the Bernstein, Simpson, and Rich patents, would not have been motivated to provide a unit dose reagent chamber containing a detergent-containing buffered solution for use in a test apparatus for detecting ATP in a test sample, by placing a detergent-containing buffered solution in the vessel of the Bernstein apparatus. The Bernstein apparatus features an open portal window and relies for its operation on the presence of a prefilter and capture membrane, and thus would not be suitable for use in ATP detection. Modification of the Bernstein apparatus to be suitable for ATP detection, by the substantial reconstruction of eliminating the prefilter and capture membrane, would result in leakage of unabsorbed fluid out of the window.

Finally, the Childs patent is relevant as a secondary consideration of non-obviousness. *Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 45 U.S.P.Q.2d 1977, 1983 (Fed.Cir. 1998) (*"Therefore, this court will address the evidence of contemporaneous invention in that context."*). The Childs patent demonstrates that others of ordinary skill in the art in 1995, seeking to provide a device for chemiluminescent detection of detergent-released ATP in a test sample and in similar possession of Bernstein, Simpson, and Rich, were *not* motivated to provide a unit dose reagent chamber for ATP detection containing a detergent-containing buffered solution or a luciferin-luciferase reagent. Childs et al. arrived at a completely different solution than that of the claimed invention. Evidence in the form of the Childs patent reduces the likelihood to below 50% that one skilled in the art would be motivated by the references to arrive at the claimed invention. The rejection can not be maintained.

1. The Examiner's Rejection

The examiner states his case of obviousness as follows:

> In view of these teachings, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide the adenosine triphosphate detection reagents as taught by the prior art references of Simpson et al. and Rich et al. within the test device structure as disclosed by the reference of Bernstein for the known and expected result of employing an alternative means recognized in the art for storing and performing a multiple step assay while providing the benefits disclosed by the reference of Bernstein when using the disclosed reagent holding system (See column 1, lines 4-28).

Office Action, January 31, 2006, page 5, lines 4-10. Bernstein summarizes the nature of the Bernstein "device" as follows:

> [A] device for a self contained solid phase immunodiffusion assay. The device is comprised of a sample collector, a tube with compartmentalized reagents and a ligand receptor capture membrane filter area. The sample collector is pushed through the seals, mixed with reagent, and then pushed into a ligand receptor reaction area wherein the tip of the sample collector contacts diffusible membranes or filters and transfers the reactants to a capture membrane wherein a ligand receptor reaction an be visualized by the naked eye.

Bernstein, abstract. The examiner has acknowledged that the Bernstein reference

> "does not disclose the use of reagents specific for the detection of adenosine triphosphate wherein the reagent is either a detergent-containing buffered solution to release adenosine triphosphate from a test sample or a luciferin-luciferase reagent."

Office Action, January 31, 2006, page 4, ¶ 3. Beyond that, the examiner's remaining findings of fact bear closer scrutiny.

1. The examiner misquotes Bernstein and is misleading when stating that,

> While the preferred embodiment of the reference of Bernstein is directed to the performance of an immunoassay detection, the reference discloses that the device is advantageous for assays that require multiple steps and require multiple reagents (See column 1, lines 13-28).

Office Action, January 31, 2006, page 4, lines 1-4 of ¶ 4. A review of the cited passage of Bernstein reveals that Bernstein makes no such statement about the Bernstein device. The cited passage is the first paragraph of Bernstein's background section, in which Bernstein articulates the problems of bringing diagnostic assay procedures

> to physicians offices and even to the home, where untrained or poorly trained individuals perform the tests usually following product insert instructions alone. These assays are useful provided they are performed properly and are safe handle for

> the user. Assays that require multiple steps, have multiple reagents, and have limited storage conditions are prone to misuse, especially if they are performed by individuals without adequate training or skills.

Bernstein, col. 1, lines 17-28. Read in context, the cited passage is merely an observation as to difficulties faced in the field of point-of-care diagnostics. The passage does not make claims specific to the Bernstein device.

2. The examiner continues with the statement,

> The reference also discloses a number of types of reagents that can be used in the device including extraction reagent and lyophilized reagents (See column 3, lines 11-28).

Office Action, page 4, lines 4-5 of ¶ 4. The passage of Bernstein at column 3, lines 11-28, is a general list of reagents frequently used in the context of ligand-receptor assays. The list omits any specific suggestion of reagents useful for chemiluminescent detection of ATP. Such a general teaching is valuable only when interpreted through the filter of one of ordinary skill in the art having in mind the development of a particular type of assay. In the Second Declaration of Steven J. Saul, Dr. Saul testifies as to how one skilled in the art of single-use ATP detection test devices would have interpreted the disclosure of Bernstein.

3. Simpson et al. is directed to a procedure for extracting ATP using a detergent-containing buffered solution to release ATP into a test solution. The procedure involves extracting ATP from a suspension of the microorganism with a cationic surface active agent (detergent), then neutralizing the cationic surface active agent. Simpson, page 4, lines 21-25. The assay of Simpson et al. is performed by pipetting ATP extraction reagents, sample, and luciferase-luciferin reagents into a standard laboratory cuvette and reading luminescent output with a luminescent photometer.

4. In Rich, a pressure roller pushes sample into a compressible plastic bag-type chamber 78 containing liquid ATP extractants. After a five minute incubation, the pressure roller compresses the chamber 78, forcing the fluid through an orifice 82 into a second plastic bag-type chamber 80, which contains luciferin-luciferase reagents. The light emitted from the luciferin/luciferase reaction is then measured by photographic exposure through a window onto Polaroid film.

2. Applicant's Rebuttal Evidence

Evidence traversing rejections, when timely presented, must be considered by the examiner whenever present. MPEP § 716.01(B). Where, as here, the examiner has determined that the evidence is insufficient to overcome the rejection, the examiner must specifically explain why the

evidence is insufficient. Id. General statements such as "the declaration is devoid of any factual evidence" are insufficient. *See,* id. Here, applicant timely submitted two pieces of evidence in rebuttal of the examiner's obviousness determination: the Second Saul Declaration (Exhibit A), and the Childs et al., U.S. 5,783,399, another patent on which David Bernstein is a named inventor (Exhibit B).

The Second Saul Declaration provides testimony as to the understanding of one of ordinary skill in the art, and should be given greater weight.

The Second Saul Declaration was submitted as rebuttal evidence in response to the non-final office action issued March 28, 2005. Although the record reflects that the declaration was entered, the examiner did not give its testimony any weight. The examiner reasoned that,

> In this case, the opinion evidence has been submitted to convey on the record that one of ordinary skill in the art would not have been motivated to modify the Bernstein apparatus for chemiluminescent detection of ATP because the modification would have made the apparatus of Bernstein unsuitable for its intended purpose of a solid phase immunodiffusion assay; the declarant is an employee of the assignee of the instant application and thus has an interest in the outcome of the application; and the declaration is devoid of any factual evidence supporting the statements within the declaration.

Final Office Action, January 31, 2006, paragraph bridging pages 8-9. For all of the reasons set forth below, applicant respectfully requests that the Board grant *de novo* review of the testimony set forth in the Second Saul Declaration.

Dr. Saul is not a party having an interest in the outcome of the application.

The examiner relies on *In re Lindell* as a basis for finding that Dr. Saul has an interest in the outcome of the application. Final Office Action, January 31, 2006, page 9. It is not clear how the facts of *In re Lindell* pertain to the instant declarant. In *In re Lindell,* the Court of Customs and Patent Appeals (CCPA) gave little credit to the affiant's testimony because the testimony was that of the patent applicant himself. The facts of this case do not rise to that level. As shown by all of the application transmittal papers of record, the oath and declaration of the original patent, and each of the supplemental oaths and declarations submitted in the current reissue application, the named inventors of the instant application have declared under oath that Dr. Steven J. Saul is not an inventor of any of the subject matter on appeal. Nor is Dr. Saul an assignee or any other party that

would qualify him as a real party in interest. As an employee of the assignee Dr. Saul is admittedly not fully at arms length, but his interests are decidedly minor when considered in the light of the facts of *In re Lindell*. Dr. Saul has given his testimony under oath and penalty of perjury. Exhibit A, ¶ 23. His relatively minor interests as a salaried employee should not be permitted to over-ride the probative value of his testimony.

Dr. Saul's testimony as to how one of skill in the art would interpret the Bernstein reference has probative value as to the factual underpinnings required to support a conclusion of obviousness.

The examiner erred in viewing the Second Saul Declaration as being no more than "declarant's opinion on the ultimate legal issue". Final Office Action, January 31, 2006, paragraph bridging page 8-9 (*citing, In re Lindell,* 155 USPQ 521 (CCPA 1967). The Second Saul Declaration offered factual evidence in an attempt to explain how one of ordinary skill in the art would have understood the Bernstein reference. The Second Saul Declaration should be considered, not as probative of the ultimate legal conclusion of obviousness, but for its testimony as to the factual underpinnings of that conclusion. *In re Alton*, 76 F.3d 1168, 1174-75, 37 USPQ2d 1578, 1582-83 (Fed. Cir. 1996) (*patent examiner erred by dismissing declaration of applicant's expert without adequately explaining how declaration failed to overcome prima facie case supporting rejection; examiner did not address expert's argument that one of ordinary skill in the art would have understood specification"*).

The examiner further erred when finding that "the declaration is devoid of any factual evidence supporting the statements within the declaration." *Id.* Such a finding is inappropriately hasty and dismissive. In point of fact, Dr. Saul, as an expert in the field, is qualified to testify as to the views of one of ordinary skill in the art as of the benefit date accorded the instant application. Exhibit A ¶¶1-3; Exhibit A1; Exhibit C ¶¶1,2,4; Exhibit C1. Dr. Saul is therefore qualified to testify as to how one of ordinary skill in the art would have understood the Bernstein reference. In particular, Dr. Saul has set forth the following factual evidence:

Fact 1. Dr. Saul testified that the Bernstein apparatus features an open portal window and relies for its operation on the presence of a prefilter and capture membrane, which would not be suitable for use in ATP detection. Modification of the Bernstein apparatus to be suitable for ATP detection

would require the substantial reconstruction of eliminating the prefilter and capture membrane, and would result in leakage of unabsorbed fluid out of the window. Exhibit A, ¶ 10.

Fact 2. Dr. Saul testified that, based on his review of the Bernstein patent, it is his view that Bernstein sought to provide a test device suitable for performing a ligand receptor assay to detect antigens, haptens, antibodies, DNA or RNA fragment, wherein the user is not required to dispense any of the reagents. Further design criteria were that all reagents be self-contained within a device that could be stored at nonrefrigerated temperatures, and which could utilize lyophilized reagents. Exhibit A, ¶ 11, citing, Bernstein, col. 2, line 56, to col. 3, line 2.

Fact 3. Referring to col. 2, lines 46-55, Dr. Saul further testified that Bernstein states that it is an object to transfer the reactants "to a reaction zone where the specific labeled reactant can be captured and visualized." Dr. Saul further stated that, at col. 1, paragraph 2, the Bernstein patent expresses the goal of eliminating any need for capital equipment such as "scintillation counters, flourometers and colorimeters in the case of radioimmunoassay, fluorescent immunoassay, and enzyme immunoassay respectively". Exhibit A, ¶ 12 (citing Bernstein, col. 2, lines 46-55).

Fact 4. It is the opinion of Dr. Saul that the Bernstein apparatus is constructed so as to accomplish the goal of performing a rapid solid phase immunodiffusion assay as, at col. 3, lines 49-52, Bernstein states that "[t]he configuration of the lower portion allows the collection device to come into physical contact with the prefilter, capture membrane or capture filter." Exhibit A, ¶ 13.

Fact 5. Dr. Saul testifies that Bernstein states that "[i]n the case where membranes or filters are used to capture the immunoreactants, it is necessary to bring the fluid containing the immunoreactants in contact with the filter or membrane." Exhibit A, ¶ 14 (*citing,* Bernstein, col. 2, lines 26-29).

Fact 6. Dr. Saul observes that Bernstein further articulates the importance of having a larger pore size filter or membrane between the swab and capture membrane to retain any unwanted cells or debris that may interfere with the assay. Exhibit A, ¶ 15 (*citing,* Bernstein, col. 2, lines 46-55).

Fact 7. Dr. Saul testified that the Bernstein apparatus is also configured so that the assay results can be observed visually through a window, which is a discrete observation portal on the front side of the lower portion of the device. Exhibit A, ¶ 16.

Fact 8. Dr. Saul testified that, in order to visualize the signal without the aid of capital equipment, it was necessary to concentrate the signal in front of the window. Exhibit A, ¶ 16.

Fact 9. Dr. Saul testified that to concentrate the signal in front of the window Bernstein had to do four things: (a) capture the labeled members of the binding pair on capture membranes 18, 19;

(b) eliminate interfering substances on a pre-filter membrane 25; (c) remove excess fluid on absorbent 17; and (d) deliver the reagents into direct proximity in front of the prefilter and reaction membranes. Bernstein, col. 3, lines 34-51. Dr. Saul further testified that, at col. 5, lines 5-8, Bernstein states, "The shape of the lower portion 10 is configured to enhance contact of the collection device tip with the pre-filter or reaction membranes." Absent each of these design features, Bernstein would not be able to achieve sufficient signal enhancement for visualization through the front window 11. Exhibit A, ¶ 17.

Fact 10. It is the opinion of Dr. Saul that it would not have been obvious to one of ordinary skill in the art in 1995 to modify the Bernstein apparatus to be suitable for chemiluminescent detection of ATP with luciferin-luciferase. Adaptation of the Bernstein apparatus for chemiluminescent detection would have required modification of the device to be suitable for use with a luminometer. Those skilled in the art would not have found a suggestion or motivation to modify the Bernstein apparatus for use with a luminometer. To do so would have contradicted Bernstein's goal of providing a rapid immunodiagnostic assay that operated independently of capital equipment. Exhibit A, ¶ 18.

Fact 11. Dr. Saul further testified that another reason those skilled in the art would not have adopted the Bernstein apparatus for use with a luminometer is that, were one to do so, the Bernstein apparatus would have become inoperable for its intended purpose of visualization of signal by the naked eye. The shape of the lower portion of the Bernstein apparatus is configured to enhance contact of the collection device tip with the prefilter or reaction membranes. Were the lower portion of the Bernstein apparatus to be modified to fit inside a luminometer, its shape would no-longer be configured to enhance contact of the collection tip with the prefilter or reaction membranes. Exhibit A, ¶ 19 (citing Bernstein, col. 5, lines 5-7).

Fact 12. Dr. Saul further testified that one skilled in the art would not have been motivated to modify the Bernstein apparatus to operate without prefilter or reaction membranes. Were the Bernstein apparatus to have been so adapted, there would be no concentration of signal in front of window 11, and the Bernstein apparatus would then be unsatisfactory for its intended purpose. Exhibit A, ¶ 20.

Fact 13. Dr. Saul further testified to his opinion that one skilled in the art in 1995 would not have been motivated to place a detergent-containing buffered solution into the vessel of the Bernstein device, because the Bernstein apparatus does not contain a closed bottom end. Dr. Saul observed

that Bernstein describes, at col. 5, lines 15-25, an "adhesive tape 12 that holds the absorbent [17] in place and applies the necessary pressure to ensure diffusion of fluid through the various layers of the ligand receptor test area." The absorbent 17 absorbs excess fluid diffusing through the membranes. By removing adhesive tape 12 by lifting tab 28 of Bernstein, the bottom end of the Bernstein device is not a closed bottom end. Exhibit A, ¶ 21 (*citing*, Bernstein, col. 5, lines 15-25).

Fact 14. It is Dr. Saul's opinion that one skilled in the art would not be motivated to undergo the substantial reconstruction of the Bernstein device that would be required to make it suitable for detecting ATP using a detergent-containing buffered solution because the bottom of the Bernstein device is not closed, so any solution would leak out the "window." Exhibit A, ¶ 22.

3. Taken as a whole, the evidence of record does not support a prima facie case of obviousness

When identifying differences between the claimed invention and the teachings of the prior art, all words in applicant's claim must be considered in judging the patentability of that claim against the prior art. MPEP 2143.03 (citing *In re Wilson*, 424 F2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970)(reversing Board's finding of obviousness where Board ignored language in the claim).

Claims 5-7 and 10

As a combination claim, claim 5 is directed to an ATP detection test apparatus containing one or more of the unit dose reagent chambers of claim 1. As a dependent claim, claim 5 incorporates all of the limitations of claim 1, and so the test apparatus of claim 5 must be suitable for conducting an ATP detection reaction in a test sample, and must also employ a moveable probe to obtain a test sample and to release one or more reagents from within a unit dose reagent chamber to a test unit. In certain embodiments, the moveable probe moves longitudinally within the test apparatus, so that the longitudinal force of the probe's movement punctures the membrane seals of the unit dose reagent chamber(s) **(claim 6)**. Claim 5 further requires that the unit dose reagent chamber portion of the test apparatus contain a detergent-containing buffered solution for releasing ATP into the solution for testing, and that a luciferin-luciferase reagent be present elsewhere within the test apparatus, such as, e.g., in the test unit portion of the test apparatus **(claim 10)**. Preferably, the test unit is transparent and has a closed bottom end **(claim 7)**. The embodiment of claim 7 positions one or more unit dose reagent chambers in the test unit portion of the test apparatus.

Critical features of the Bernstein test apparatus make it decidedly unsuitable for chemiluminescent detection of ATP, and unsuitable for use in an ATP detection reaction requiring a detergent-containing buffered solution. Although the examiner acknowledges that the Bernstein test apparatus has been designed to perform an immunoassay, not to detect ATP, the examiner asserts that Bernstein's col. 1, lines 13-28, and col. 3, lines 11-28 support a broader interpretation of Bernstein. Final Office Action, January 31, 2006, page 4. As discussed above, the cited passages from Bernstein are inconsistent with that assertion. Bernstein's list omits any specific suggestion of reagents useful for chemiluminescent detection of ATP. Neither of these general statements broaden the scope of suitability of Bernstein's test apparatus to chemiluminescent detection of detergent-released ATP. By the examiner's reasoning, one skilled in the art would have been motivated to modify the Bernstein apparatus for any multi-step assay by placing ***any*** reagents into the vessels of Bernstein. In taking this position, the examiner does not address the specific language incorporated into claim 5 from claim 1. Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the question of obviousness. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81, 93 (Fed.Cir. 1986).

There is no suggestion or motivation to combine the cited references

The rejection should be withdrawn as lacking any rationale as to how or what would have suggested or motivated the skilled artisan to modify the Bernstein apparatus to provide the claimed invention. Merely alleging that the references can be combined or modified does not make the resulting combination obvious unless the prior art also suggests the desirability of the combination. MPEP 2143.01.

> ***There is no motivation to combine references where, as here, the proposed modification would change the principle of operation of the prior art apparatus of the primary reference, and would render the prior art apparatus unsatisfactory for its intended purpose.***

It is well established that no suggestion or motivation to combine is present where the proposed modification would change the principle of operation of the prior art reference. MPEP 2143.01 (p. 2100-132), *citing, In re Ratti*, 270 F.2d 810, 813, 123 USPQ 349, 352 (CCPA 1959) (*obviousness rejection reversed where suggested combination of references would require a substantial reconstruction and redesign of the elements shown in the primary reference as well as a change in the basic principle under which the primary reference construction was designed to*

operate). It is also well established that there is no suggestion or motivation to combine the references where the proposed modification would render the prior art unsatisfactory for its intended purpose. MPEP 2143.01 (p. 2100-131), *citing, In re Gordon,* 733 F.2d 900, 221 USPQ 1124 (Fed. Cir. 1984) (BPAI's conclusion of *prima facie* obviousness reversed based on finding that, were prior art device to be turned upside down, it would have been inoperable for its intended purpose).

Bernstein is directed to an apparatus for performing a solid phase immunodiffusion assay in which a proteinaceous antibody or receptor is bound as a capture ligand to a membrane positioned over a hole at the bottom end. Bernstein operates by delivering ligand from the test sample to the capture membrane, whereby a ligand:receptor interaction is formed between the ligand and the capture agent and a signal is concentrated on the membrane sufficient to visualize the signal through a window 11. At least two objectives are fundamental to the teachings of Bernstein.

First, one of ordinary skill in the art in 1995, reading the Bernstein, Simpson, and Rich patents, would not have been motivated to provide a unit dose reagent chamber containing a luciferin-luciferase reagent by placing luciferin-luciferase in the vessel of the Bernstein apparatus, because the Bernstein apparatus is not suitable for chemiluminescent detection of ATP, and because modification of the Bernstein apparatus for chemiluminescent detection of ATP would have made the Bernstein apparatus unsuitable for its intended purpose of a solid phase immunodiffusion assay. Second Declaration of Dr. Steven J. Saul (Exhibit A, "Second Saul Declaration"), ¶9. The Bernstein apparatus is designed so that assay results can be observed visually through window 11, which is a discrete observation portal on the front side of lower portion 10. (See Figs. 5 of Bernstein). In fact, Bernstein states clearly that the Bernstein apparatus is designed to operate independently of instrumentation such as scintillation counters, flourometers and colorimeters. Bernstein, col. 1, para. 2; Second Saul Declaration, ¶12. To concentrate the signal in front of the window Bernstein must do four things: (a) capture the labeled members of the binding pair on capture membranes 18, 19; (b) eliminate interfering substances on a pre-filter membrane 25; (c) remove excess fluid on absorbent 17; and (d) deliver the reagents into direct proximity in front of the prefilter and reaction membranes. (*See,* Bernstein col. 5, lines 5-8: *"The shape of the lower portion 10 is configured to enhance contact of the collection device tip with the pre-filter or reaction membranes."*) Bernstein, col. 3, lines 34-51; Second Saul Declaration, ¶17. Absent each of these design features, Bernstein would not be able to achieve sufficient signal enhancement for visualization through the front window 11. Second Saul Declaration, ¶17.

It is an indicia of nonobviousness where, as here, the suggested combination of references would require a substantial reconstruction and redesign of the elements shown in the primary reference, as well as a change in the basic principle under which the primary reference construction was designed to operate. In order to modify the Bernstein device for use with luciferin-luciferase, the Bernstein device would have had to have been adapted for chemiluminescent detection, i.e., by modifying the devise to be suitable for use with a luminometer. Were the Bernstein device to have been so adapted, there would be no concentration of signal in front of window 11, and the Bernstein apparatus would then be unsatisfactory for its intended purpose. Second Saul Declaration, ¶¶18-20.

Second, one of ordinary skill in the art in 1995, reading the Bernstein, Simpson, and Rich patents, would not have been motivated to provide a unit dose reagent chamber containing a detergent-containing buffered solution for use in a test apparatus for detecting ATP in a test sample, by placing a detergent-containing buffered solution in the vessel of the Bernstein apparatus. The Bernstein apparatus features an open portal window and relies for its operation on the presence of a prefilter and capture membrane, and thus would not be suitable for use in ATP detection. Modification of the Bernstein apparatus to be suitable for ATP detection, by the substantial reconstruction of eliminating the prefilter and capture membrane, would result in leakage of unabsorbed fluid out of the window. Second Saul Declaration, ¶10 and ¶¶20-22.

Claims 7 and 10

For related reasons, the examiner has not established a *prima facie* case of obviousness with respect to claims 7 and 10. The inventions of claims 7 and 10 are directed to the combination of the unit dose reagent chamber and test apparatus of claim 5, along with a closed bottom end, transparent test unit at one end of the test apparatus. The bottom end of the Bernstein device, in contrast, features window 11, and is not closed. Second Saul Declaration, ¶10 and ¶¶20-22; *see also,* Bernstein, claim 1, element h)(*"means forming a hole in said tube . . ."*). One skilled in the art would not be motivated to place a detergent containing buffered solution into the Bernstein apparatus. The bottom of the Bernstein device is not closed, so any solution would leak out the hole at the bottom of the test apparatus.

Claims 1, 2, and 12

The unit dose reagent chamber of claim 1 contains a detergent-containing buffered solution and/or a luciferin-luciferase reagent, for use in a test apparatus that would be suitable for performing

an ATP detection assay that employs one or both of these reagents. To consider the invention as a whole, the rejection must account for the recitations of the preamble. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430, 1432 (Fed. Cir. 1990) (reversing Board's rejection of all claims as obvious where differences between reference and claims lie solely in the functional language in the preamble reciting an intended use for the machine).

When stating that,

> [t]he reference of Bernstein discloses a unit dose reagent chamber for use in a test apparatus (See Figure 4)"

the examiner ignores crucial claim limitations, and thus does not consider the claimed invention as a whole. *See,* Office Action, March 28, 2005, page 4, lines 708. The proper inquiry is not whether Bernstein discloses *"a unit dose reagent chamber for use in a test apparatus"*, but rather whether Bernstein discloses *"unit dose reagent chamber for use in a test apparatus for the detection of adenosine triphosphate (ATP) in a test sample"*. Bernstein does not disclose a test apparatus suitable for detecting detergent-released ATP by chemiluminescent reagents.

Secondary indicia of non-obviousness reduces the likelihood that one skilled in the art would be motivated to combine the prior art references to below the required 50% threshold..

A decision to maintain a rejection must show that the decision is based on the totality of the evidence. MPEP 2143.01. The examiner must consider not only those references cited, but also any and all evidence that supports patentability of applicant's invention, including any evidence of secondary considerations submitted by the applicant in rebuttal. *Id.* Evidence establishing a secondary indicia of non-obviousness can include evidence that others of ordinary skill in the relevant art arrived at alternative solutions. *Monarch Knitting Machinery Corp.,* 45 USPQ2d at 1983. General skepticism of those in the art that does not amount to "teaching away" is still relevant and persuasive evidence of non-obviousness. *Monarch Knitting Machinery Corp.,* 45 USPQ2d at 1984.

In the present case, there is at least a 50% likelihood that one skilled in the art, in possession of the cited references and seeking to solve the problem of detecting ATP using one or more of a detergent and a luciferin-luciferase reagent, would have chose *not* to modify the Bernstein test apparatus, but rather would have pursued an alternative solution. Evidence of the fact that one skilled in the art was at least as likely to pursue different options is found in US Patent 5,783,399,

which was filed on November 17, 1995 by inventors Mary Ann Childs, Gregory K. Shipman, William P. Trainor, Erick Gray, and David Bernstein ("Childs et al.", Exhibit B).

We do not know what actually motivated Childs et al. but even if we did it would be irrelevant to the issue of obviousness. *Amazon.com, Inc. v. Barnesandnoble.com, Inc.*, 239 F.3d 1343, 57 U.S.P.Q.2d 1747 (Fed.Cir. 2001). The relevant inquiry is what a hypothetical ordinarily skilled artisan would have gleaned from the cited references at the time of the invention. *Id.* The written disclosure of the Childs et al. patent is *prima facie* evidence establishing that it is just as likely that the skilled artisan, seeking to solve the problem of providing a device for chemiluminescent detection of detergent-released ATP in a test sample, would have arrived at a completely different solution than that encompassed by the claimed invention. Given evidence of an alternative solution by those skilled in the art in 1995, a *prima facie* case of obviousness has not been established to a preponderance of the evidence. *Monarch Knitting Machinery Corp.*, 45 USPQ2d at 1982 (reversing the district court's finding of obviousness where *"All of these references stated the problem as preventing hook breakage at high speeds. Each of these references proposed a different solution. Thus, this evidence creates a genuine issue as to whether those of ordinary skill would have had a motivation to combine needles with varying stem segment heights to form a trend."*).

The inventors of the Childs et al. patent sought to use chemiluminescent methods to detect ATP when monitoring surfaces for bacterial contamination. Exhibit B, col. 1, lines 6-56. Childs et al. recognized that luciferin-luciferase reactions of the firefly had been used previously for detecting threshold levels of microorganisms. Exhibit B, paragraph bridging col. 1-2. But Childs et al. also recognized that lyophilized luciferase-luciferin reagent could be unstable at room temperature during long term storage, and considered it to be unstable after liquid reconstitution over short time intervals. *Id.*

Given that all of the cited references of Bernstein, Simpson, and Rich predated the filing date of Childs et al., applicant is entitled to the legal presumption that the cited references were available to Childs et al. , especially in view of their collaborative relationship with co-inventor David Bernstein. Yet when faced with the problem of using luciferin-luciferase to detect ATP on a test surface as an indication of bacterial contamination, the inventors of the Childs patent did not choose to modify the Bernstein reference. The inventors on the Childs patent chose a completely different solution to that problem.

The device that Childs et al. discloses for accomplishing this goal is a lateral flow type device having a lateral flow membrane on a solid support strip, having a sample portion, a reagent portion, and a fluid reservoir on the test strip that breaks in response to finger pressure to cause carrier fluid to flow from the reservoir across the lateral flow strip. The solution arrived at by Childs et al. included either drying a detergent onto the sample portion or reagent portion of the test strip (col. 5, lines 7-10 and 61-65), or placing a detergent into the carrier fluid in the fluid reservoir (col. 3, lines 31-33 and col. 6, lines 4-5). The solution of Childs et al. further includes applying a reconstituted solution of luciferin-luciferase to the membrane filter strip and drying *in vacuo* (col. 8, lines 49-56).

Thus, the Childs et al. patent makes it clear that, despite possession of the cited references, one of skill in the art would not necessarily have arrived at the solution of providing a unit dose reagent chamber containing either a detergent-containing buffered solution or a luciferin-luciferase reagent. It has not been established to a preponderance of the evidence, i.e., that it is more than 50% likely, that one skilled in the art would have been motivated to modify or combine Bernstein, Simpson, and Rich to arrive at the unit dose reagent chamber, test apparatus, and test unit of applicant's claimed invention.

In light of the above, applicant submits that the rejection can not be maintained, because the rejection lacks rationale as to why the skilled artisan would modify the Bernstein apparatus in keeping with the disclosures of Simpson and Rich, given that such modifications would have required substantial reconstruction of the Bernstein apparatus, changed its principle of operation, and rendered it unsuitable for its intended purpose. In addition, the Childs et al. patent is evidence that those skilled in the art, in possession of the same prior art references in 1995 and seeking to solve the problem of providing a device for chemiluminescent detection of ATP in a test sample, would have been just as likely to seek a completely different solution. Thus, the totality of the evidence does not support a conclusion that there is a greater than 50% likelihood that the claimed invention would have been obvious to one skilled in the art in view of Bernstein, Simpson, and Rich.

B. <u>Rejection under 35 U.S.C. § 103(a): Bernstein in view of Simpson, Rich, and Matsumoto</u>

Claims 10, 14, 15, 17-19, 23, 24 and 26 have been rejected under 35 U.S.C. § 103(a) as not being patentable over Bernstein (US 4,770,853) in view of Simpson et al. (EP 0 309 184;

"Simpson") and Rich et al. (US 3,666,631; "Rich") and taken further in view of Matsumoto et al. (JP 7-59555). Applicant respectfully requests that the rejection be reversed.

Matsumoto et al. is not directed to a separate sealed reagent chamber or to the use of multiple, aligned reagent chambers in a test unit. The Matsumoto et al. container is a pocket-type, microbial incubator, not a reagent test apparatus. The Matsumoto et al. container provides for the separation of a "liquid substance containing an indicator" in a sealed package, from a dry, inactive microorganism tablet in the bottom end of the incubator. The Matsumoto et al. incubator solves the problem of keeping the dry microorganism apart from the liquid until the collecting bead with the sample is used to inoculate the moistened microorganisms.

The Matsumoto et al. apparatus is not directed to the detection of ATP or AP in a luminescent method within the test unit and does not have or suggest single or multiple, separate, aligned unit dose reagent chambers in a test unit, nor does it have a transparent test unit, with a reagent chamber to be removedly secured from one end of the test unit for separate insertion into a photometer for observation (see application Figs. 5 and 7).

The Bernstein, Simpson, and Rich references have been discussed above. The above arguments and the testimony set forth in the Second Saul Declaration relating to the Bernstein, Simpson, and Rich references apply equally to the invention of claims 10, 14, 15, 17-19, 23, 24, and 26, and are hereby incorporated by reference. In addition, Childs et al., US Patent 5,783,399 (Exhibit B) is secondary indicia that one skilled in the art, having possession of Bernstein, Simpson, Rich, and Matsumoto, would not have been motivated to arrive at the solution of the claimed invention.

All of the cited references of Bernstein, Simpson, Rich, and Matsumoto predated the filing date of Childs et al. Applicant is thus entitled to the legal presumption that the cited references were available to Childs et al., especially in view of their collaborative relationship with co-inventor David Bernstein. Although Childs et al. sought to provide a device for detecting ATP on a test surface as an indication of bacterial contamination, the inventors of the Childs patent did not choose to modify the apparatus of the primary Bernstein reference according to the disclosures of Simpson, Rich, and Matsumoto. The inventors on the Childs patent chose a completely different solution to that problem, namely, a lateral flow diffusion assay.

Childs et al. establishes that there is at least a 50% likelihood that one skilled in the art, in possession of the cited references and seeking to solve the problem of detecting ATP using one or

more of a detergent and a luciferin luciferase reagent, would have chosen ***not*** to modify the Bernstein test apparatus. but rather to have pursued an alternative solution. Thus, the examiner has not established that those skilled in the art, in possession of the cited references, would have necessarily arrived at the claimed invention. Other options were available, creating an at least 50% probability that that one skilled in the art would have come up with an alternative solution to that of claims 10, 14, 15, 17-19, 23, 24, and 26.

Respectfully submitted:

Date. March 9, 2007

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VIII. Claims Appendix

1. (twice amended) A unit dose reagent chamber for use in a test apparatus for the detection of adenosine triphosphate (ATP) [or alkaline phosphatase (AP)] in a test sample, and wherein a moveable probe is employed to obtain a test sample and to release reagents from the reagent chamber to a test unit, which unit dose chamber comprises:

a) a cylinder having a one open end and an other opposite open end;

b) a probe-puncturable membrane seal over the one end and the other end of the cylinder to form a sealed compartment; and

c) a reagent composition [for use in the detection of the test sample and sealed] within the sealed compartment, which composition consists essentially of and is selected from the group consisting of:

i) a detergent-containing buffered solution to release adenosine triphosphate (ATP) [or alkaline phosphatase (AP)] from the test sample into the solution for testing; and

ii) [a reaction stopping solution having a pH of 8 to 11; and

iii)] a luciferin-luciferase [or phosphatase substrate] reagent [tablet].

2. (original) The chamber of claim 1 wherein the membrane seal comprises aluminum foil.

3. (cancelled).

4. (twice amended) A unit dose reagent [The] chamber [of claim 1] for use in a test apparatus for the detection of adenosine triphosphate (ATP) in a test sample and wherein a moveable probe is employed to obtain a test sample and to release reagents from the reagent chamber to a test unit, which unit dose chamber comprises;

a) a cylinder having a one open end and an other opposite open end;

b) a probe-puncturable membrane seal over the one end and the other end of the cylinder to form a sealed compartment; and

c) a reagent composition within the sealed compartment, which composition consists essentially of and is selected form the group consisting of;

wherein the reagent composition is selected from the group consisting of (i) a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing; and (ii) a luciferin-luciferase reagent, and wherein the reagent composition includes a pH indicator.

5. (twice amended) In combination, the chamber of claim 1 in a test apparatus for the detection of adenosine triphosphate (ATP) [or alkaline phosphatase (AP)] in a test sample, wherein the reagent composition is a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing, which test apparatus includes a luciferin-luciferase [or phosphatase substrate] reagent for reaction with the released adenosine triphosphate (ATP) [or alkaline phosphatase (AP)] in the solution.

6. (amended 2/03) The combination of claim 5 wherein the test apparatus [includes] further comprises a longitudinally moveable probe to puncture the membrane seals[to carry out the test].

7. (amended) The combination of claim 5 wherein the test apparatus [includes] further comprises a closed bottom end, transparent test unit at the one end of the test apparatus, and wherein one or more unit dose reagent chambers are longitudinally positioned in the test unit.

8. (cancelled).

9. (cancelled).

10. (three times amended) The combination of claim 7 wherein the reagent composition is a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing [sealed compartment comprises the buffered-detergent solution] and wherein said test apparatus includes a luciferase and a luciferin reagent [in tablet form] at the bottom end of the test unit.

11. (cancelled).

12. (twice amended) The chamber of claim 1, wherein the reagent composition is selected from the group consisting of i) a detergent-containing buffered solution to release adenosine triphosphate (ATP) from the test sample into the solution for testing; and ii) a luciferin-luciferase reagent, and wherein the reagent composition includes a biological buffer solution to optimize a reaction for the detection of adenosine triphosphate (ATP) [or alkaline phosphatase (AP)].

13. (cancelled).

14. (three times amended) A test apparatus for the detection of adenosine triphosphate (ATP) [or alkaline phosphatase (AP)] in a test sample, by luminescence [or color], which test apparatus comprises:

a) a longitudinal test apparatus housing having a one end and an other end;

b) a moveable probe within the housing to collect a test sample and arranged to puncture a membrane seal;

c) a transparent test unit having a one end and a closed bottom end extending from the one end of the housing for use in detecting luminescence [or color] in the test sample, and a first reagent

[tablet] composition to detect adenosine triphosphate (ATP) [or alkaline phosphatase (AP)], by [color or] luminescence, at the closed bottom end; and

d) one or more unit dose reagent chambers longitudinally-positioned in the test unit, which reagent chamber comprises:

i) a cylinder having a one open end and an other opposite open end;

ii) a probe-puncturable membrane seal at and over the one end and the other end of the cylinder to form a sealed compartment; and

iii) a second reagent composition for use in the detection of adenosine triphosphate (ATP) [or alkaline phosphatase (AP)] in the test sample and sealed within the sealed compartment, which reagent composition comprises a buffered solution to release adenosine triphosphate (ATP) [or alkaline phosphatase (AP)] from the test sample into the solution for subsequent reaction with the first reagent [tablet] composition.

15. (original) The apparatus of claim 14 wherein the membrane seal comprises aluminum foil.

16. (cancelled).

17. (twice amended) The apparatus of claim 14 wherein the test unit has an open top end [with threads] and a closed bottom end and is detachably [removedly, threadably] secured to one end of the test apparatus.

18. (original) The apparatus of claim 14 wherein the one end of the test unit is sealed with a probe-puncturable membrane.

19. (twice amended) The apparatus of claim 14 wherein the sealed compartment comprises a buffer-detergent solution and a luciferase and a luciferin substrate, as a reagent [tablet], is at the bottom end of the test unit.

20. (cancelled).

21. (cancelled).

22. (cancelled).

23. (twice amended) A transparent test unit for use in a test apparatus for the detection of a test sample, which test unit comprises: a one end; a closed bottom end; a probe-puncturable membrane over the one end; and the one end having means for detachably securing the test unit to the test apparatus and the test unit having one or more unit dose reagent chambers, which unit dose chamber comprises:

a) a cylinder having a one open end and an other opposite open end;

b) a probe-puncturable membrane seal over the one end and the other end of the cylinder to form a sealed compartment: and

c) a reagent composition for use in the detection of the test sample and sealed within the sealed compartment; and [The test unit of claim 21] wherein the test unit includes a luciferin-luciferase reagent [tablet].

24. (added; amended) The apparatus of claim 19, wherein said luciferase and said luciferin reagent are in tablet form.

25. (cancelled).

26. (added) The test unit of claim 23, wherein said luciferin-luciferase reagent is a luciferin-luciferase tablet.

27. (added; cancelled).

28. (added; cancelled).

29. (added; cancelled).

30. (added; amended) A unit dose reagent chamber for use in a test apparatus for the detection of alkaline phosphatase (AP) in a test sample, and wherein a moveable probe is employed to obtain a test sample and to release reagents from the reagent chamber to a test unit, which unit dose chamber comprises:

a) a cylinder having a one open end and an other opposite open end;

b) a probe-puncturable membrane seal over the one end and the other end of the cylinder to form a sealed compartment; and

c) a reagent composition within the sealed compartment, which composition consists essentially of and is selected from the group consisting of: i) a detergent-containing buffered solution to release alkaline phosphatase (AP) from the test sample into the solution for testing; and ii) a reaction stopping solution having a pH of 8 to 11; and wherein the reagent composition includes a pH indicator.

Claims 31-45 (added; cancelled).

IX. Evidence Appendix

The following evidence was submitted in the application pursuant to U.S.C §§ 1.130, 1.131, or 1.132, and is relied on in the present appeal.

Exhibit No.	Evidence	Statement setting forth where in the record evidence was entered in the record by the Examiner
A	Second Declaration of Dr. Steven J. Saul ("Second Saul Declaration")	Entered with Applicant's Amendment filed 9/28/05, as Exhibit A thereto
B	Childs et al., US Patent 5,783,399, issued July 21, 1998	Entered with Applicant's Amendment filed 9/28/05, as Exhibit B thereto
C	Declaration of Dr. Steven J. Saul under 37 C.F.R. § 1.132 ("First Saul Declaration")	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B thereto
C1	Curriculum vitae of Dr. Steven J. Saul (Exhibit 1 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B1 thereto
C2	Stanley, P.E., *Extraction of Adenosine Triphosphate from Microbial and Somatic Cells, Methods in Enzymology*, 133:14-22 (1986) (Exhibit 2 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B2 thereto
C3	Andreotti et al., WO 92/20781, November 26, 1992 (Exhibit 3 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B3 thereto
C4	Wood, US Patent No. 5,283,179, 1994 (Exhibit 4 to First Saul Declaration)	Entered with Amendment filed 3/25/04, as Exhibit B4 thereto
C5	Optimization of the Firefly Luciferase Assay for ATP (Webster, J.J., and Leach, F.R., *Jour. Applied Biochemistry*, 2:469-479, 1980) (Exhibit 5 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B5 thereto
C6	Effect of Solvents on the Catalytic Activity of Firefly Luciferase (Kricka, L.J. et al., *Archives of Biochemistry and Biophysics*, 217(2), 1982) (Exhibit 6 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B6 thereto
C7	U.S. Patent No. 5,004,684, Simpson et al, 1991 (Exhibit 7 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B7 thereto

Exhibit No.	Evidence	Statement setting forth where in the record evidence was entered in the record by the Examiner
C8	US Patent No. 4,303,752, Kolehmainen et al., 1981 (Exhibit 8 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B8 thereto
C9	Denville Scientific Inc., *Research Products Catalog 1991,* pages 1, 2, 15 (Exhibit 9 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B9 thereto
C10	Denville Scientific Inc., *Research Products Catalog,* 1995, pages 1, 2, 16 (Exhibit 10 to First Saul Declaration)	Entered with Applicant's Amendment filed 3/25/04, as Exhibit B10 thereto
D	U.S. Provisional Application 60/001,081, filed July 12, 1995	
E	U.S. Provisional Application 60/007,585, filed November 27, 1995	
F	Examiner's Interview Summary, March 23, 2006.	Examiner's Interview Summary, March 23, 2006.

X. Related Proceedings Appendix

None.